

## STEREOTACTIC RADIOSURGERY USING THE LEKSELL GAMMA KNIFE: CURRENT TRENDS AND FUTURE DIRECTIVES

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### 1. ABSTRACT

Stereotactic radiosurgery is the extremely precise administration of a radiation dosage in three-dimensional space to treat an increasingly broad spectrum of intracranial and skull-base lesions. 455 patients with various indications were treated using the 201 Source Co-60 Leksell Model "B" Gamma Knife® at Louisiana State University Health Sciences Center in Shreveport, Louisiana. 273 (60.2%) patients received radiosurgery as the first line of treatment for their disease. The mean Karnofsky Performance Score (KPS) of the patients was 70. Cerebral metastases were the main indications for radiosurgery at our center accounting for 27% of the patients, while meningioma, AVM, trigeminal neuralgia, movement disorders, and primary CNS malignant tumors were the other indications. Our institutional experience and results indicate that low incidence of complications coupled with a high tumor control rate makes Gamma Knife stereotactic radiosurgery a viable option for patients who must undergo neurosurgery. As the Gamma Knife continues to prove itself as a first-line treatment of many complex brain disorders, new indications for this technology will continue to emerge, further broadening the scope of patient care.

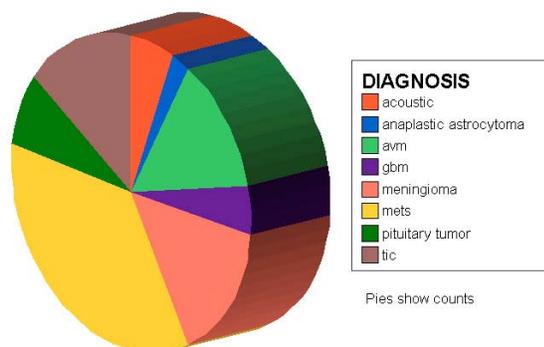
### 2. INTRODUCTION

Stereotactic radiosurgery is the extremely precise administration of a radiation dosage in three-dimensional space to treat an increasingly broad spectrum of intracranial and skull-base lesions. The strategy of radiosurgery is to use a high radiation dose to the volume of the target lesion to effect biological damage with minimal radiation to the surrounding tissue and without opening the skull.

### 3. HISTORICAL ASPECT

Stereotactic radiosurgery became known to the world in 1908 (1) in a paper by Horsley and Clarke. They described this method to study the structure and function of the cerebellum in the monkey's brain. A three-dimensional frame was used that could be fixed to the skull, thereby creating a system in which any point within the skull could be defined by an external three-point coordinate system. In 1947, Speigel and Wycis (2) modified the apparatus to one that had a separate coordinate system within the brain defined by the anterior and posterior commissures of the third ventricle. Lars Leksell, in 1951(3) was the first to introduce the concept of radiosurgery. He and his co-

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**Figure 1.** Pie chart depicting various indications for Gamma knife radiosurgery at the LSUHSC- Shreveport.



**Figure 2.** Leksell Gamma Knife model "C" at the LSUHSC- Shreveport.

workers coupled their stereotactic guiding device with an orthovoltage x-ray tube that had the capability to rotate into arc planes around the patient's head. In 1967 the construction and installation of the first Gamma Knife was completed. This prototype used the advantages of geometric focusing, multiple sources disbursed over a large area and patient positioning to produce very small, disc shaped lesions in brain nuclei and white matter tracts. The first patient treated with the machine had craniopharyngioma. Later, in 1975, Leksell designed a second Gamma Knife that had more spherical dose distribution power. Leksell deliberately used the term "radiosurgery" to stress that, in spite of the physical agent used, this technique had little to do with radiotherapy. Whether the instrument in question is a scalpel, diathermy, laser, or ionizing radiation, the procedure nonetheless remains neurosurgical because of its precision and nature of the targeted pathology. Today, Gamma Knife radiosurgery is practiced in more than 75 facilities in the United States, many of which are located in university medical centers. The patients are usually specifically selected, treated, and followed by a multidisciplinary team effort.

### 4. PATIENT DEMOGRAPHICS

Between January 2000 and January 2003, 455 patients with various indications were treated using the 201 Source Co-60 Leksell Model "B" Gamma Knife<sup>®</sup> (Elekta Instruments, Atlanta, GA) at Louisiana State University Health Sciences Center in Shreveport, Louisiana. The patient age ranged between 13 and 87 years (mean age = 57

years). 273 (60.2%) patients received radiosurgery as the first line of treatment for their disease, while 182 (39.8%) had previous surgeries and/or radiation therapy. The mean Karnofsky Performance Score (KPS) of the patients was 70 (range = 50 to 100). Cerebral metastases were the main indications for radiosurgery at our center accounting for 27% of the patients, while meningioma, AVM, trigeminal neuralgia, movement disorders, and primary CNS malignant tumors were the other indications (Figure 1).

### 5. TECHNIQUE OF GAMMA KNIFE RADIOSURGERY

All patients were admitted to the "day surgery" unit of the hospital on the day of the procedure. A Leksell Model 'G' stereotactic head frame was applied to the heads of the patients under conscious sedation and local anesthesia using a mixture of lidocaine (0.5%), bupivacaine (0.5%), and sodium-bi-carbonate. The patients were then transferred to the MRI for imaging. Target localization of the lesion was done on 1-mm thick, Gadolinium- enhanced, axial MR slices of the brain obtained with the Spoiled Gradient Recalled Acquisition in Steady State<sup>®</sup> sequence (GE Inc. Milwaukee, WI). The images were transferred to the Gamma Knife computer via ethernet.

#### 5.1. Dosimetry

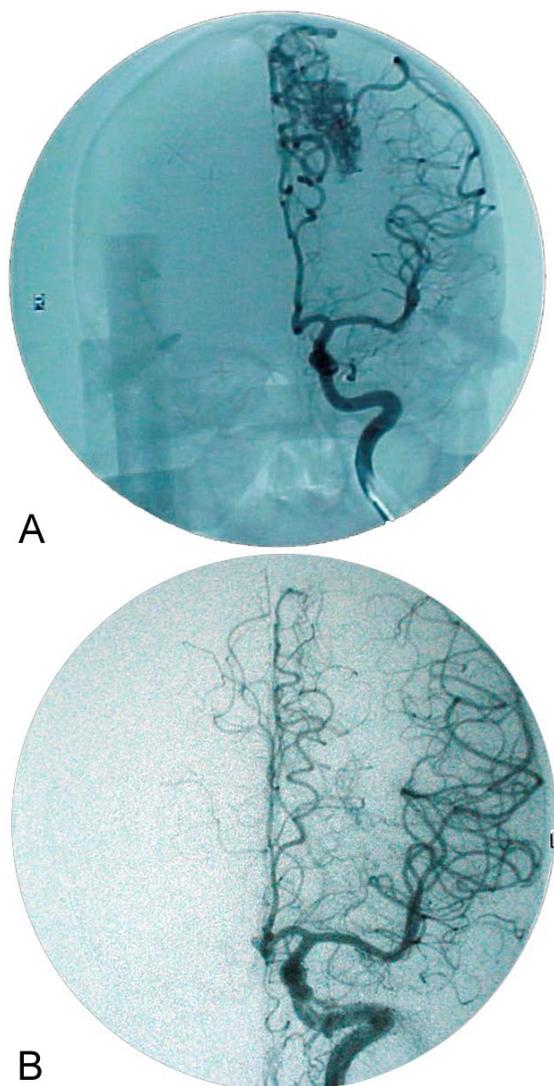
Radiosurgery dose-planning was done using the Leksell Gamma Plan software, version 5.3 (Elekta Instruments, Atlanta, GA). The neurosurgeon, radiation oncologist, and radiation physicist determined target localization, dose-planning, and dose prescription jointly. The maximal prescription dose ranged from 21 Gy to 90 Gy depending upon the pathology, location, and volume of the target (mean dose = 37 Gy). Mean marginal dose was 17 Gy (range = 10.5 Gy to 45 Gy). Radiosurgery was administered using the Leksell Gamma knife (Figure 2).

### 6. INDICATIONS OF GAMMA KNIFE RADIOSURGERY

#### 6.1. Cerebral arteriovenous malformations

Gamma Knife has proved to be particularly useful in the treatment of arteriovenous malformations (AVMs) in the brain that were previously considered inoperable due to their size, critical locations and/or deep venous drainage. Attempts have been made in the past to elucidate the histopathological changes in the AVM vessels after radiosurgery (4). The earliest change demonstrated was endothelial damage as evident by a denuded endothelium or by disruption and separation of the endothelial lining from the underlying vessel wall. Even though progressive endothelial proliferation and thrombosis are considered to be the main factors that lead to the occlusion of the irradiated arteriovenous malformation in response to radiation (5), the alteration in the structure and function of the microvasculature in response to radiation is believed to also lead to radiation-induced vascular damage (6). Radiosurgery at standard clinical doses appears to inflict little injury to normal brain vessels. Radiosurgery seems to induce a proliferative vasculopathy within the

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**Figure 3.** A: Pre- and B: 24 month post-radiosurgery arteriograms of a 21-year-old female presenting with motor strip AVM.

blood vessels of an AVM. Preliminary studies performed by irradiating laboratory cultured immortalized human cerebral endothelial cells with gamma rays in our laboratory suggested that endothelial cell adhesion molecules (ECAMs) are upregulated within 24 to 96 hours of exposure of endothelial cells to gamma irradiation. These facts indicate the activation of a definite cascade eventually leading to complete endothelial cell damage at 96-120 hours post radiation. Contrary to our expectations, cellular apoptosis did not seem to play a significant role in the endothelial damage in response to radiosurgery. No significant changes observed in the Caspase-3 assays and total cellular disruption at 120 hours show that the damage is acute as opposed to the stepwise pattern of programmed cell death associated with apoptosis (7). Therefore, radiation induced tissue injury may represent a series of events which are mediated at least in part by activation of the leukocyte-endothelial adhesion cascade, rather than a

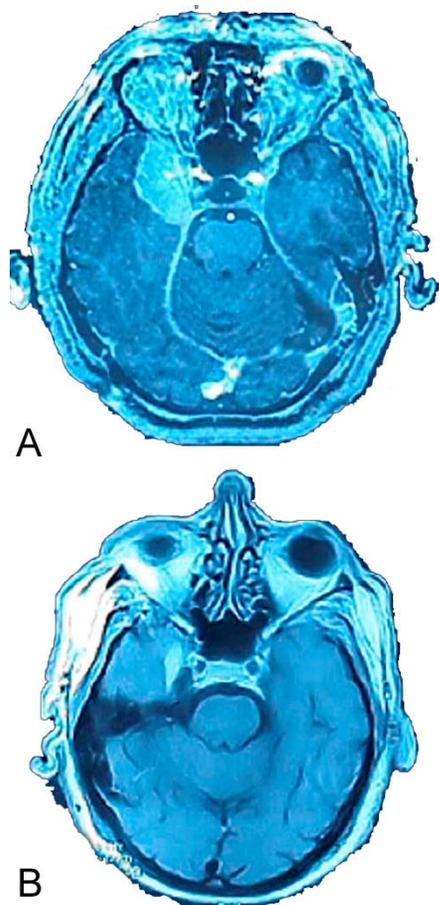
direct effect of gamma-irradiation on endothelial viability. Most interestingly, this prompts us to consider whether the tissue destruction following gamma knife irradiation is not instead mediated by the promotion of a local inflammatory response that is leukocyte dependent in nature.

### 6.1.1. LSU Experience

Forty-one patients with cerebral arteriovenous malformation (AVM) received radiosurgery over 36 months. The age range was 21 to 65 years (mean age = 36 years). Thirteen patients had previous bleed (one or two), while 28 presented with headaches, seizures, and/or visual disturbances. The location of the malformation was as follows: occipital (n=11), temporal (n=8), frontal (n=7), motor strip (n=7), parietal (n=3), thalamic (n=4), and brainstem (n=1). The volume of the AVM nidus varied from 2.4 cc to 18.6 cc (mean = 9.8 cc). All of the patients had radiosurgery as the primary treatment for the malformation. Radiosurgery planning was performed using MRI and digitally subtracted cerebral arteriograms in all the patients. The mean marginal dose delivered to the nidus was 18 Gy (range = 16 Gy to 25 Gy). Twenty-four months follow-up is available on 12 patients, and the other 18 have been followed for at least a year. Six patients showed complete disappearance of the nidus at 24 months (Figures 3A & 3B). Two patients (4.8%) had a hemorrhage in the AVM at 5 and 7 months following treatment. MRI and angiogram at the time of the bleed revealed a reduction in the size of the nidus compared to that at the time of radiosurgery. One improved with conservative therapy while the other underwent surgical excision at an outside center. None of the patients had any complication related to radiation during the follow-up period.

### 6.2. Cerebral metastases

Brain metastases develop in up to 50% of all patients with cancer and can pose serious health problems (8). In most series, the use of fractionated whole brain radiation therapy (WBRT) extends survival by 3 to 5 months. Many physicians harbor a nihilistic approach to patients with multiple brain metastases, most likely due to perceived poor outcomes despite available treatments. Traditionally, surgical resection has rarely been offered to patients with multiple metastases because the morbidity of resection in multiple brain locations was believed to be excessive and the risk of developing additional tumors was perceived to be high. The powerful radiobiologic effect of stereotactic radiosurgery was initially used to replace the therapeutic benefits provided by surgical resection. Using single-session stereotactic irradiation of the defined tumor, radiosurgery was performed to arrest tumor growth and reduce parenchymal brain edema. The growth potential of metastatic brain tumors following radiosurgery was shown to be significantly diminished. The initial results of Phase I and II studies have already been published (9), while a Phase III trial of radiosurgery for multiple metastases has also been completed (10). This trial had to be discontinued prematurely at 60% accrual, according to the "60% stopping rule", due to the remarkable difference in the local tumor control rates. They found that the tumor control rate in the group receiving radiosurgery was significantly higher than the group receiving XRT alone.



**Figure 4.** A: Pre- and B: 12 month post-radiosurgery contrast enhanced MR axial images of a 74-year-old male with recurrent cavernous sinus meningioma.

### 6.2.1. LSU Experience

Between January 2000 and January 2003, 96 patients with 182 tumors diagnosed as cerebral metastases were treated with stereotactic radiosurgery using the Leksell Gamma Knife. Lung carcinoma (50%) was the most common primary, followed by breast (12%) and melanoma (10%). Thirty-nine patients had solitary metastases, while 57 had multiple tumors. Fifty-five patients (57.2%) (100 tumors) received radiosurgery as the primary modality, while 41 (82 tumors) had additional external beam whole brain radiation. The tumor volume ranged from 0.5 cc to 29 cc (mean = 5.8 cc). The mean marginal dose prescription to the tumor was 16 Gy (range = 13 Gy to 19 Gy). The median follow-up was 11 months. Thirty-two patients (34.4%) were alive at last follow-up, and 64 (65.6%) had died. Twenty-five deaths (26.04%) were reported to be due to progressive brain disease, while 39 deaths (73.9%) were due to the uncontrolled primary. The overall survival was calculated using the method of Kaplan-Meier. The mean overall survival for the series was 8 months (range = 1 to 19 months) and the median survival was 6 months (95% CI). The actuarial overall survival rates at 6,12, and 18 months, respectively, were  $46.5 \pm 0.06\%$ ,  $28.8 \pm 0.06\%$ , and  $17.3 \pm 0.06\%$ .

### 6.3. Benign tumors

In the last 25 years, many patients with benign tumors have undergone radiosurgery. It is believed that the radiobiologic effect on benign tumors is a combination of both cytotoxic and delayed vascular effects (11). The success rate in achieving a tumor control for radiosurgery has been shown to be 90% in the published series (12). In addition, the benefits of radiosurgery for acoustic tumors include a higher preservation of hearing and other cranial nerve functions (13,14). Our results, though early, seem to support this belief.

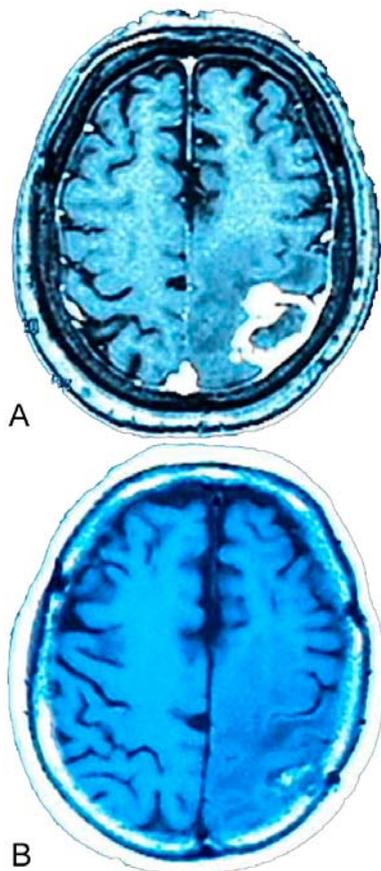
#### 6.3.1. LSU Experience

##### 6.3.1.1. Meningioma

Twenty-six patients with skull base meningiomas received stereotactic radiosurgery. Twenty-one patients (80.8%) were females and 5 were males. The patient age ranged from 35 to 74 years (mean = 58.6 years). Headache (n=10) was the most common symptom followed by diplopia (n=7), syncope, and dizziness (n=6). Other less frequently noticed symptoms were limb weakness (n=2), uni-ocular blindness (n=2), and hearing deficit (n=2). Fifteen patients (57.7%) received radiosurgery as the primary modality, while 11 had previous excisions (1 to 3). Two patients had a total previous excision, while 9 others had a sub-total resection. The maximal tumor dose varied from 24 Gy to 30 Gy (mean = 27 Gy). Twenty-five patients were alive at the last follow-up while one had died. Twelve patients (46.2%) experienced improvement in their pre-existing symptoms, eleven (42.3) continued to remain unchanged, while 3 (11.5%) had worsening. Maximal improvement (4 out of 7) was noticed in the patients with external ocular muscle weakness, while headache (3 out of 10) was the least improved symptom. Postoperative contrast-enhanced MRI studies were utilized to calculate and compare the tumor volume. A significant reduction in tumor volume was defined as at least 20% reduction in the volume of enhanced area, while a failure was labeled with 10% persistent increase in the contrast-enhancing area on follow-up imaging studies. Seventeen patients (65.4%) in the current study showed a reduction in the tumor volume (Figures 4A, 4B) while 7 (26.9%) continued to remain unchanged. Two patients (7.7%) showed increase in the tumor size and were labeled failures. Both of these patients underwent subsequent surgery and one was diagnosed to have atypical meningioma (as suggested by a high mitotic index and presence of atypical cells) on histopathology.

##### 6.3.1.2. Acoustic tumors

Fifteen patients with vestibular schwannomas were treated using Gamma Knife stereotactic radiosurgery at this center. Three patients had a previous resection, while 12 had radiosurgery as the first option. The tumor dose of 13 Gy was administered in all of the patients as per the established protocol. All patients were alive at the last follow-up. Seven patients (46.6%) had a 20% to 30% regression in the size of the tumor, one patient had a complete disappearance of the tumor at 6 months and one tumor had a documented central necrosis in response to radiosurgery. All others showed no evidence of growth in the follow-up MRI scans. The control rate, therefore, was 100% for the treatment of acoustic tumors with



**Figure 5.** A: Pre- and B: 6 month post-radiosurgery contrast enhanced MR axial images of a 73-year-old female with recurrent GBM.

radiosurgery at our center. One patient had symptoms of trigeminal dysfunction following radiosurgery, and 6-months post-radiosurgery MRI showed evidence of pontine edema at the trigeminal nerve root entry zone. This patient became asymptomatic following oral steroids for a period of 6 weeks.

### 6.4. Primary CNS malignancies

In high-grade malignant gliomas, there is a heterogeneous cellular composition of the target tissues to be irradiated. At any given time, the tumor cells exist in various phases of the cell cycle and have varying degree of hypoxia. While a single high-dose irradiation has the greatest desirable biological effect on rapidly proliferating cells, normal tissue too are at a higher risk of injury (15). The initial criticism of the use of radiosurgery for gliomas therefore included its focal radiation delivery and its delivery during a single session (16). However the intense radiobiologic effect of a single session radiation cell-kill, regardless of the mitotic phase, has been the argument of physicians in favor of the use of radiosurgery for malignant gliomas (17). The radiosurgical treatment for malignant tumors, though, is very different than that for AVM or benign tumors. This is because, although the contrast-enhanced tumor volume identified on imaging can be irradiated by a conformal margin isodose during

radiosurgery, the malignant tumor cells beyond this contrast enhancement remain “outside” the radiosurgery volume. This is not to say that these cells receive “no” irradiation but they exist in the “fall-off” zone of the treated volume at the selected isodose. Therefore, radiosurgery to the selected contrast enhanced volume can provide potential benefit to the patient by improving the likelihood of local control.

### 6.4.1. LSU Experience

Eighteen patients with malignant glial brain tumors were treated with stereotactic radiosurgery at LSUHSC-Shreveport, Louisiana. Pathology revealed anaplastic astrocytoma (AA) in 5 patients and glioblastoma multiforme (GBM) in 13 patients. Patient age ranged from 28 to 73 years (mean = 48.6 years). Temporal lobe was the most common site (33.3%). Eleven patients had previous whole brain irradiation using external beams (30-55 Gy), and 4 patients received chemotherapy (BCNU). The mean follow-up period was 12 months, and median follow-up was 10 months post-radiosurgery (range = 5 to 25 months). At last follow-up, 9 patients (50%) were alive, while 9 had died. Tumor-control was achieved in 13 patients (72.2%), while failure was encountered in 5 patients (27.8%). The mean overall survival for patients with AA was 16 months and for those with GBM was 14 months. Four of the five tumors (80%) in the AA group and 9/13 (69%) were controlled at the last follow-up (Figures 5A, 5B). The actuarial tumor control rate by Kaplan-Meier method at 12 months was  $53.3 \pm 0.2\%$  for AA and  $23.4 \pm 0.1\%$  for GBM, respectively. Younger patient age and smaller tumor volume were significant predictors of a favorable outcome. Tumor control and disease-controlled survival (DCS) were significantly better for the AA group ( $p=0.002$ ).

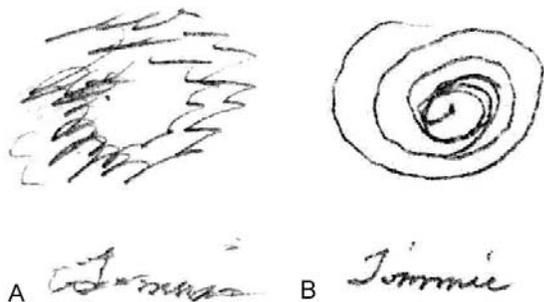
### 6.5. Trigeminal neuralgia

Radiosurgery is the least invasive surgical procedure for trigeminal neuralgia (18,19). We, as well as others, have noted no systemic morbidity. Young *et al* have reported that only 1 of their 60 patients had increased facial sensory loss, and the Pittsburgh group found a 10% rate of partial facial numbness.

### 6.5.1. LSU Experience

Fifteen patients with the diagnosis of trigeminal neuralgia received stereotactic radiosurgery at our center. Ten patients had typical idiopathic neuralgia, while 5 had post-herpetic neuralgia. The mean patient age was 63 years (age range = 45 to 79 years). Eleven patients had radiosurgery as the first surgical procedure for pain control, and 4 had previous microvascular decompression surgery. Follow-up was available on 11 patients. Eight patients (53.3%) had complete relief from pain and were withdrawn from all medications (excellent result) at a median 2-month period (range = 1 day to 3.5 months). Four others (26.6%) had more than 50% relief from pain, but continued taking regular medication, though in a smaller dosage (good result). One patient died of cardiac cause within one month of the procedure. Three patients (20%) had no change in the frequency or intensity of the pain attacks, even after undergoing 2 months of the procedure. These patients were labeled as treatment failures. Considering the patients with

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**Figure 6.** A: Pre-radiosurgery and B: 48 month post-radiosurgery “Archimedes Spirals” and handwriting sample of 84-year-old female treated for essential tremors.

excellent and good results combined, the success rate for Gamma Knife radiosurgery for trigeminal neuralgia at our center was approximately 80%. This is comparable to that published in the literature from well-established centers. We had no incidence of facial numbness for our patients. The absence of infection, CSF leakage, anesthesia complications, facial weakness, and brainstem injury has established radiosurgery as an attractive surgical alternative for many patients with trigeminal neuralgia.

### 6.6. Movement disorders

In radiosurgery thalamotomy, imaging definition alone is used for lesion placement. Because of the absence electrophysiological information and inability to confirm the target site intra-operatively, most surgeons reserve this procedure only for patients with medical disorders that preclude invasive procedures. The typical delay for the clinical results is 1-18 months (20) and is an additional disadvantage. Nevertheless, radiosurgery is constantly gaining recognition as definitive options for patients with ET. In their series, Niranjana *et al* reported that the radiosurgical lesions performed for ET or MS-related tremor with more than 6 months follow-up provided 100% reduction in tremor (21). We recently performed a successful Gamma Knife radiosurgery thalamotomy for essential right-hand tremor in a 79-year-old woman at our center without any complications. She had a follow-up MRI at 12 months post-radiosurgery that clearly showed the evidence of radiosurgery lesioning in the left thalamus on T-2 weighted axial images. At the patient’s next visit (approximately 14 months after radiosurgery), she detected a remarkable reduction in the tremor. She was subjected to a complete neurological exam and tremor test including the Archimedes spiral drawings and handwriting tests. It was noted that both the drawings and the handwriting of the patient had improved from the pre-radiosurgery grade III (Figure 6A) to grade I (Figure 6B). The tremor was not evident at rest or on intention.

#### 6.6.1. Others

Radiosurgery has been performed at our center for various other intracranial lesions, such as pituitary tumors, jugular foramen schwannoma, hemangiopericytoma, and pleomorphic adenocarcinoma. However, the number of cases is not large enough to analyze and present the results for each of these clinical entities.

## 7. FUTURE DIRECTIONS AND APPLICATIONS

The scope of radiosurgery has been ever expanding in the past decade. It has been applied to treat various pain syndromes. Young *et al* found a 50% reduction in pain in two-thirds of patients using a 4 mm isocenter at a maximal dose upto 160 Gy (22). Internal capsule radiosurgery has been experimentally used for the treatment of obsessive-compulsive disorders. Isolated reports have been published documenting the effectiveness of radiosurgery in the management of parasitic brain infestations (hydatid cyst) and sphenopalatine neuralgia. With the development of radiation sensitizers and improved delivery vehicles, radiosurgery of infectious brain lesions may become an alternative to prolonged antimicrobial therapy. In addition, the antiepileptic effect of radiosurgery appears to be independent of the angiographic response in patients with vascular malformations. These results suggest that radiosurgery can reduce seizure frequency without the need to obtain actual histological destruction.

## 8. CONCLUSIONS

Rapid developments in neuroimaging, stereotactic techniques, and robotic technology in the last decade have contributed to improved results and wider applications of stereotactic radiosurgery. The low incidence of complications coupled with a high tumor control rate makes Gamma Knife stereotactic radiosurgery a viable option for patients who must undergo neurosurgery. As the Gamma Knife continues to prove itself as a first-line treatment of many complex brain disorders, new indications for this technology will continue to emerge, further broadening the scope of patient care.

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